We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Structural Analogy — Direct Similarity Versus Topographical Complementarity

Paweł Kafarski and Magdalena Lipok

1. Introduction

The era of rational drug design started with conclusion of Paul Ehrlich that substances, which are used to dye bacteria for their visualization under the microscope, must interfere with bacterial cells. If so, some of them may interfere lethally and therefore Ehrlich started systematic search on the action of various dyes (and further other organic compounds) on bacterial growth. In that manner he had discovered first synthetic antibacterial agent – arsphenamine, *Salvarsan* (Figure 1), a cure for syphilis [1]. These studies initiated the concept of chemotherapy and brought him the Nobel Prize in 1908. Paul Ehrlich studied medicine at the University of Wrocław (then Breslau) and therefore this chapter is dedicated to him and his achievements.

Gerhard Domagk who, at the Bayer Laboratories of the IG Farben conglomerate in Germany, studied the effect of new synthetic dyes on streptococci continued his idea [3]. One of the dyes, namely sulfonamidochrysoidine, namely *Prontosil Rubrum* (Figure 1) for its red color, appeared to be promising antibacterial agent in mice [4]. Researchers at the French Pasteur Institute found, at the end of 1935, that prontosil is metabolized to sulfanilamide, which acts as real antibiotic. It inhibits multiplication of bacteria by acting as antimetabolite of p-aminobenzoic acid in the folic acid metabolism cycle. Sulfanilamide is considered as isosteric and isoelectronic analogue of p-aminobenzoic acid because its three dimensional and electronic structure resembles closely that of the metabolite (Figure 2).

This discovery started an era of effective and popular technique called structural analogy, which has been popularly used for designing and development of innovative drugs.

In 1939 Domagk received the Nobel Prize in Medicine for discovery of the first drug effective against bacterial infections but he was forced by Nazi regime to refuse the prize. He received it after the war in 1947.
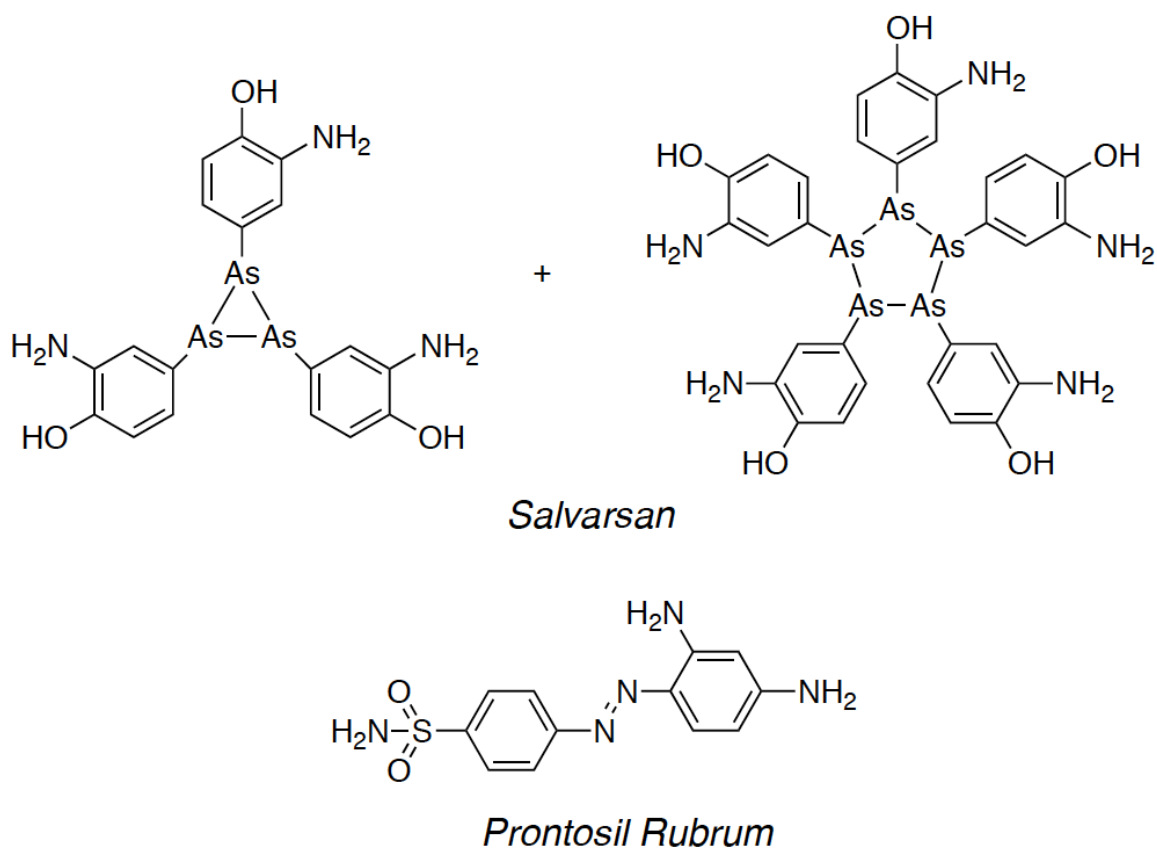
Figure 1. Structures of *Salvarsan* (actual oligomeric structure is differing from that proposed by Ehrilch [2]) and *Prontosil Rubrum*
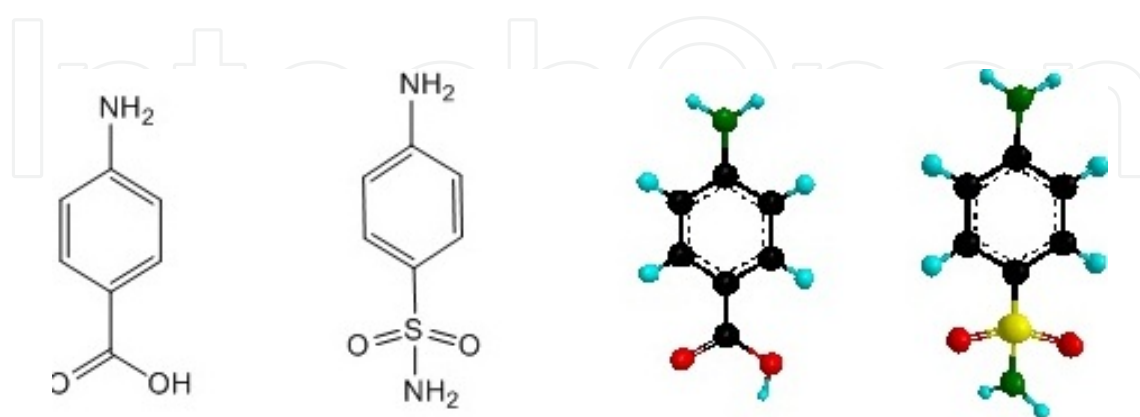
Figure 2. Structures of p-aminobenzoic acid and sulfanilamide

## 2. Direct similarity as a basic tool of structural analogy

Concept of structural analogy gave an impetus to general search for antimetabolites of therapeutic utility. The principal approach involves introduction of minor changes to the chemical structure of chosen metabolite by replacement of its specific functional groups by related ones, most likely isosteric and isoelectronic. The invention of anticancer drug, methotrexate, is one of the oldest examples of successful implementation of this methodology [5]. Methotrexate is N-methylated aminopterine, a formal antimetabolite of folic acid. In the case of aminopterine and methotrexate hydroxyl group of pteridynyl fragment of folic acid is replaced by amino moiety (Figure 3).
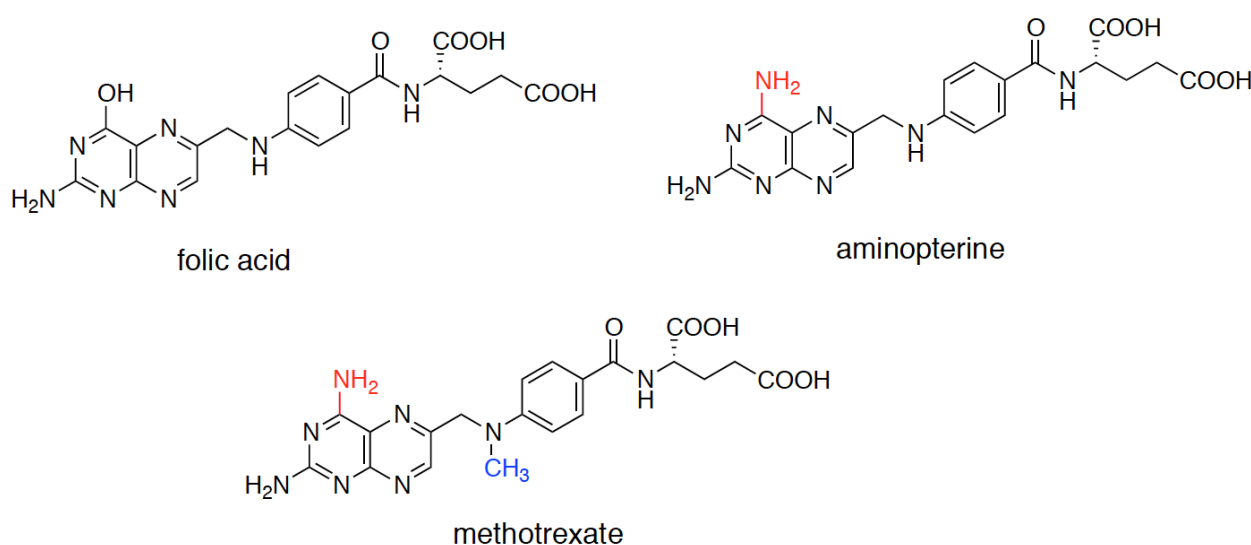
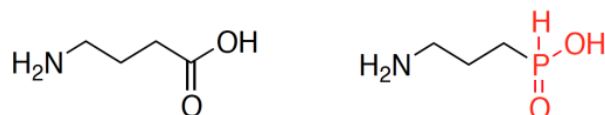**Figure 3.** Structures of folic acid and its analogues

A good example how minute modifications introduced to the structure of the drug change the activity of the new molecule is a comparison of the activity of analogues of morphine [6]. Morphine is an opioid analgesic drug and the main psychoactive component of opium. In order to avoid its addictive action a wide variety of structural analogues of this drug have been synthesized, with representative ones shown in Figure 4. This example also illustrates that the application of the theory of structural analogy is quite cumbersome because it requires synthesis of many new structurally related chemical entities in order to evaluate how small structural changes introduced to parent molecule affect its biological activity.

Sometimes quite surprising results are obtained as it is illustrated by the activity of phosphinic acid analogue of γ–aminobutyric acid (GABA). GABA is a chief inhibitory neurotransmitter in mammalian central nervous system. There are two classes of GABA receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are ligand-gated channels, whereas $GABA_B$ are G protein-coupled receptors. In order to understand their physiologic functions a molecular tools able to switch one of the receptors when not influencing the other one are required. The activating affinity
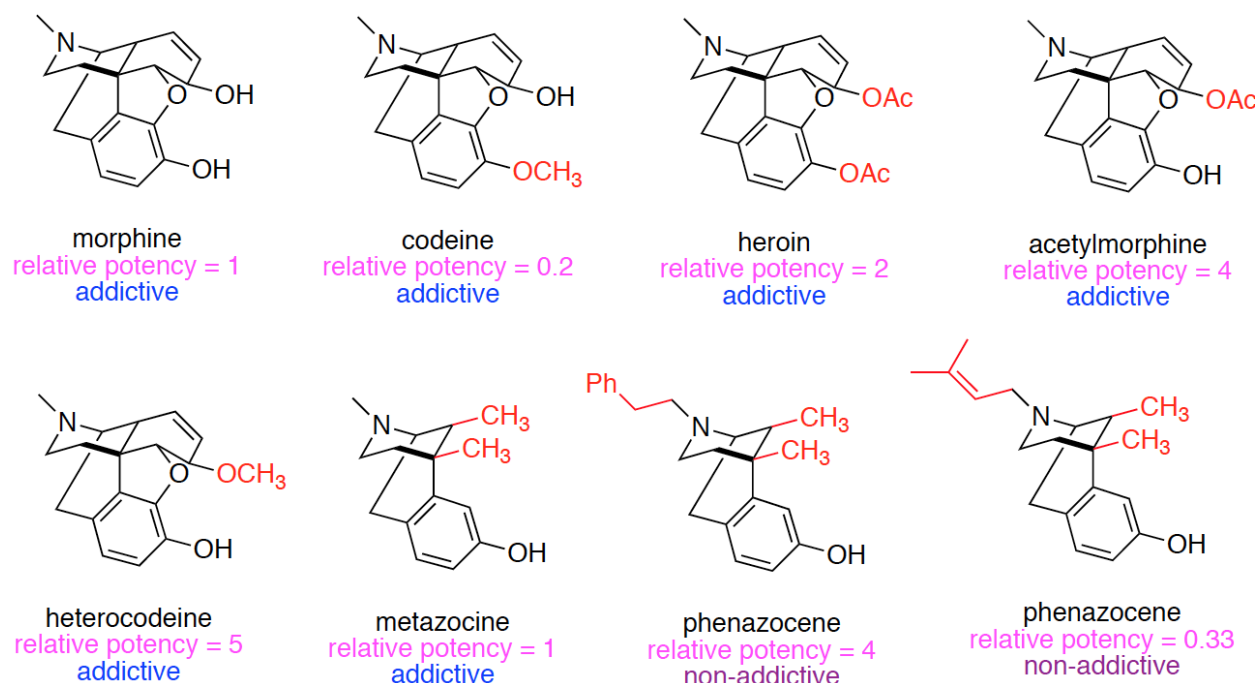
Figure 4. Structure-activity relationship in morphine analogues

of GABA to the two receptors is equal and values 20 nM. Fortunately, its phosphinic acid analogue is 4,500 times more selective towards GABA$_B$ receptor, with affinity of 1 nM [7].


Figure 5. GABA and its phosphinic acid analogue

Theory of structural analogy is most commonly used to modify structures of the known drug molecules. This process is called drug optimization and is done in order to enhance drug secondary properties such as: absorption, stability, distribution, metabolism and toxicity. This is also cumbersome and time-consuming process. However, there are some indications that help to achieve the goal. A useful example is modification of geldanamycin, an antimelanotic compound isolated from *Streptomyces hygroscopicus*. It binds to Heat Shock Protein 90 and alters its function inducing degradation of proteins that are mutated in tumor cells. Despite its potent antitumor potential, geldanamycin presents several major drawbacks as a drug candidate, with hepatotoxicity being the most dangerous. That is why *Kosan Biosciences* introduced improved geldanamycins obtained by replacement of methoxyl at the 17 position by allyla-mine group (Figure 6) [8]. This modification additionally improved solubility of the drug.

Another example is the modification of the structure of valacyclovir, an antiviral agent produced by *GlaxoSmithKline*, active against *Herpex simplex* and *Herpex zoster*. It is a prodrug since the hydrolysis of *L*-valine releases popular antiviral agent – acyclovir. Replacement of

valine by aminocyclopropanecarboxylic acid (Figure 6) improves the stability of the prodrug and results in the increase of its oral availability [9].
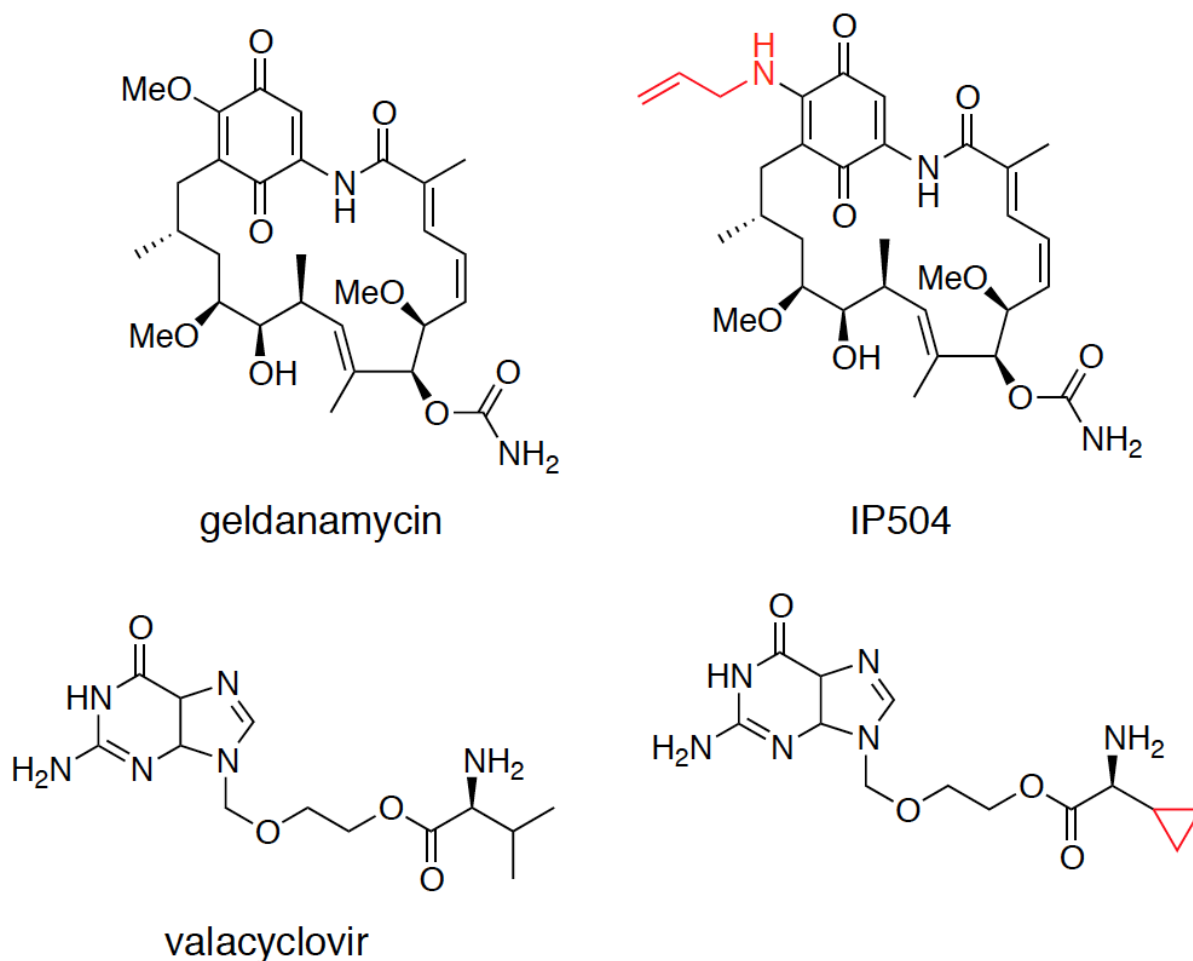
Figure 6. Improvement of drug action by use of structural analogy approach

In some cases small modification of the drug structure led unexpectedly to change of its mode of action [10,11]. This might be considered as both shortcoming and advantage of this technique. For example, modifications of promethazine (Figure 7), which is a first generation of H1 receptor antagonist being used medically as antihistamine antiemetic to prevent motion sickness, nausea or vomiting and itching associated with allergies, led to chlorpromazine, which works on a variety of receptors in the central nervous system, producing anticholinergic, antidopaminergic, antihistaminic and weak antiadrenergic effects. Thus, it is used to treat psychotic disorders such as schizophrenia and bipolar disorder. Another minute modification of promethazine structure led to imipramine, which is mainly used for the treatment of major depression, panic disorder and enuresis (inability to control urination).

A new dimension to the structural analogy approach was brought by development of combinatorial chemistry. It is essentially a collection of techniques, which allow rapid and parallel synthesis of multiple compounds at the same time and then to select the compound of the
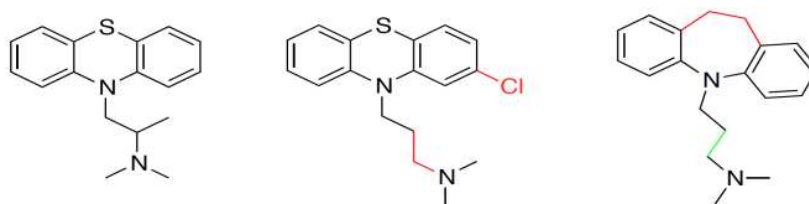
Figure 7. Structures of promethazine, chlorpromazine and imipramine

highest activity. These techniques are now largely automated, what causes that collections of compounds (libraries) are made easily and might be fast evaluated towards chosen molecular target. Thus, application of combinatorial chemistry enables to overcome long-lasting and cumbersome stepwise synthesis of structural analogues of certain drug candidate [12].

In humans, 23 matrix metalloproteinases (MMPs) have been identified. The association of MMPs with a variety of pathological states has stimulated impressive efforts over the past 20 years to develop synthetic compounds able to block efficiently the uncontrolled activity of these enzymes [13]. Extremely potent inhibitors of MMPs have been developed, but in most cases these compounds act as broad spectrum ones [14]. The development of selective inhibitors for each MMP is a difficult goal to achieve because of the high structural similarity between the different members of this enzyme family [15]. Synthesis based on a combinatorial approach and screening of libraries containing pseudopeptides with an isoxazole motif in the P1′ position (Figure 8) has led to the identification of a highly selective inhibitor of the macrophage elastase (MMP-12), a potential drug against atheroma plaque rupture [16].
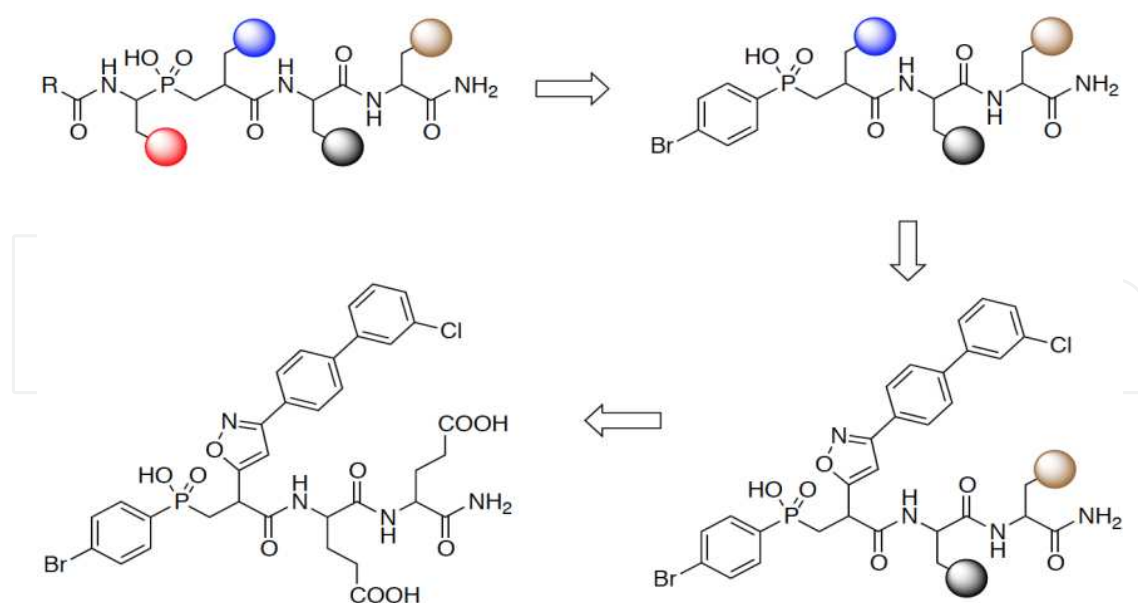

Figure 8. Discovery of selective inhibitor of MMP-12 by combinatorial approach

Another modification of structural analogy approach is to use protein structures found by X-ray crystallography or NMR as a template to design potential drugs by computer-assisted

procedures. Idea of this technique is similar to combinatorial chemistry in that the libraries of structural analogues of certain drugs are designed. Then the computer "docks" each molecule from the chosen library into target's binding site and scores its geometric and electrostatic fit. There are quite a big number of docking programs available and all of them predict the possible binding of a ligand by calculating the contribution of certain types of interactions to overall affinity. Thus, it is possible to analyze *in silico* drug activity from the first principles of quantum mechanics and to determine the key interactions crucial for inhibitory activity [17]. Finally, most promising compounds are being synthesized and their physiologic activity is evaluated.

Tuberculosis is one of the most wide-spread infections with the highest mortality among diseases caused by a single pathogen [18]. Due to the multi-drug resistance strains of *Mycobacterium tuberculosis*-disease's causative agent, novel antituberculosis drugs are rapidly needed. It releases significant amounts of proteins to the extracellular space, among which glutamine synthetase is one of the most abundant. Glutamine synthetase is the major enzyme involved in nitrogen metabolism in plants and bacteria. It catalyzes reaction of glutamate with ammonium ion, in the presence of ATP, which leads to glutamine [19]. Additionally, in case of pathogenic mycobacteria it is crucial for biosynthesis of cell wall component, poly-L-glutamate/glutamine. X-ray structure of bacterial glutamine synthetase complexed with phosphinothricin [20], a potent inhibitor of this enzyme, was used for computer-aided structure-based design of the inhibitors (Figure 9), in which the methyl group of phosphinothricin was chosen as the modification site. Thus, the classic structural analogy approach was used. Among 25 structures predicted by used LUDI program [21] the compounds with amino and hydroxyl moieties introduced into the phosphinic acid portion of the lead molecule were found to interact with ammonium binding site in the active cleft of the enzyme and also appeared to be the effective inhibitors of glutamine synthetase [22].
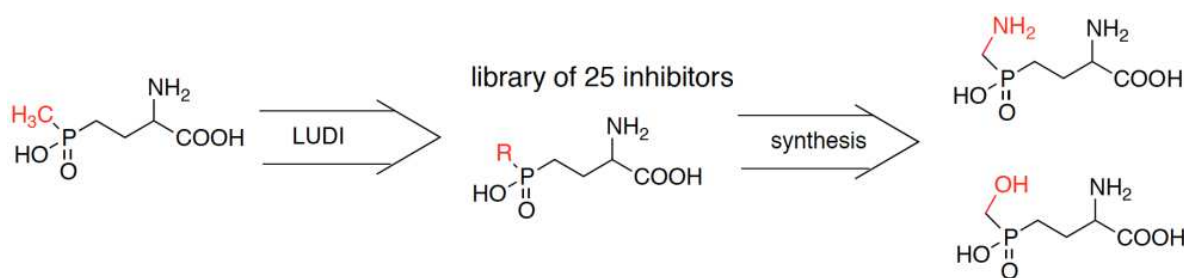
Figure 9. Inhibitors of glutamine synthetase predicted by computer-aided technique basing on phosphinothricin structure

It is worth to mention that not all the structures designed by program had been synthetically available and that chemical synthesis still is the most challenging step in innovative drug development as illustrated in Figure 10 summarizing approaches to obtain these two analogues of phosphinithricin.
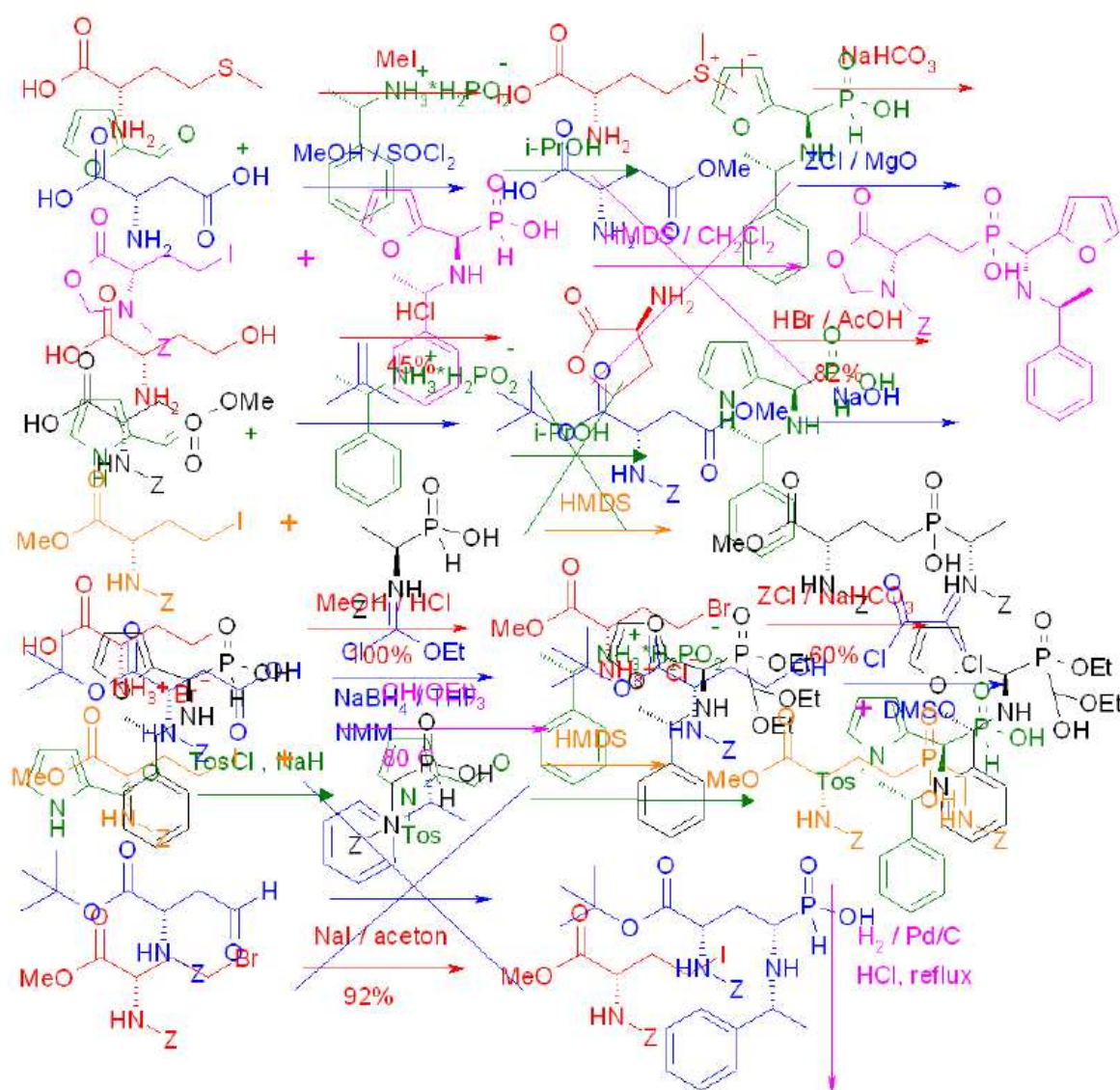
Figure 10. Synthetic routes to analogues of phosphinothricin

3. Modification of structural analogs — How far the structure of drug may differ from the parent molecule

Methotrexate was developed to inhibit mammalian folate metabolism and thus act as anti-cancer drug. Its discovery is considered as one of the milestones in modern chemotherapy [23]. It is used to treat various cancers but also severe psoriasis and rheumatoid arthritis. Interestingly, first developed to treat malignancies it is now used to treat gynecological problems [24]. As shown in Figure 11, the structure of methotrexate could be divided into some blocks, for which structural analogues might be designed. In the first step these modifications are minute ones and mainly relay on the replacement of chosen fragments by isosteric and isoelectric ones

as represented by such drugs as: *Leucovorin*, *Talotrexin*, *Tomudex* and *Alimta* [25-27]. Further modifications lead to the drugs less and less resembling folic acid, as it is well demonstrated by the structures of antimalarial drugs *Trimethoprim and Cycloguanil* [28].
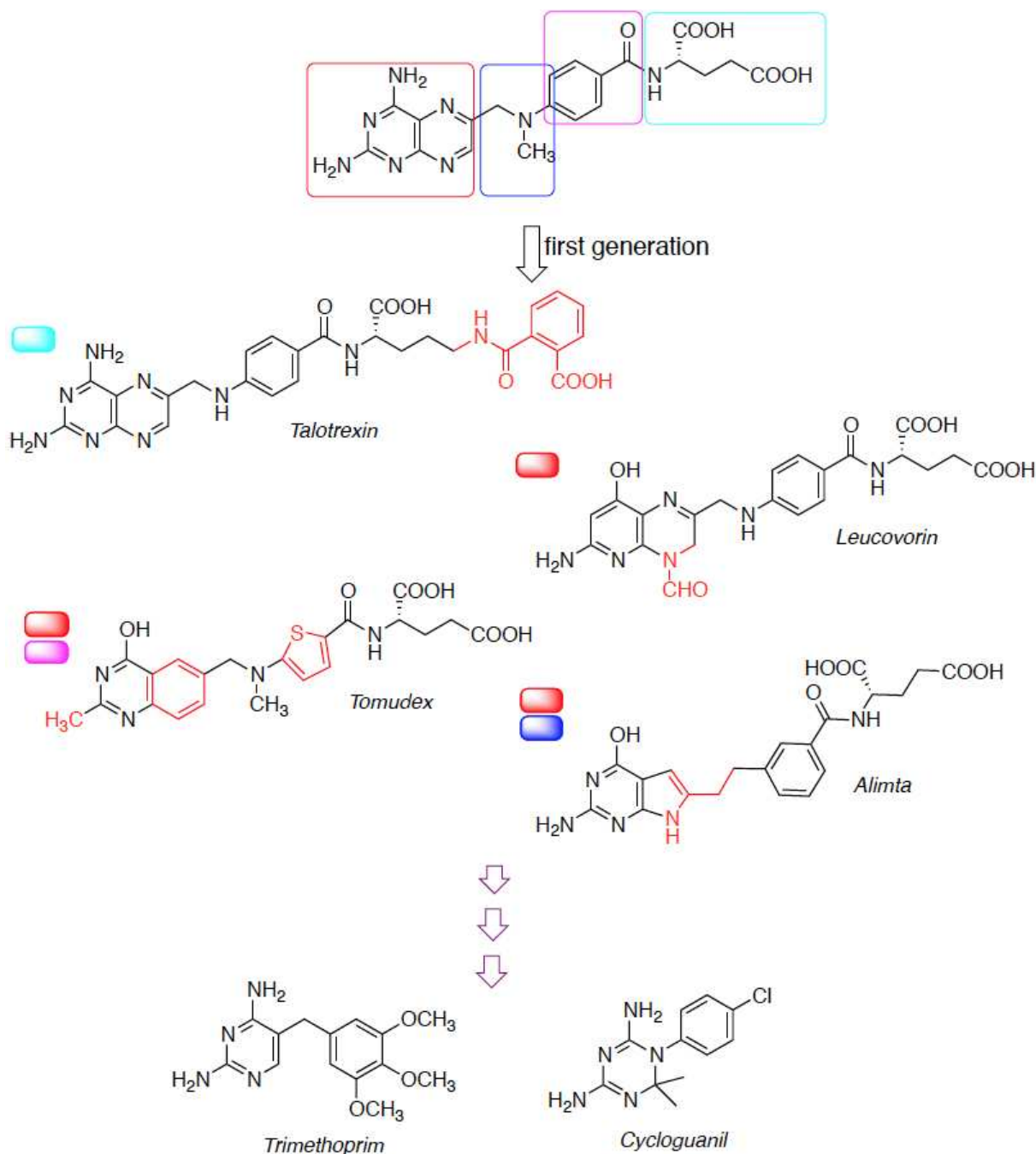
Figure 11. Analogues of methotrexate

There is a growing medical need for new antibacterial agents due to increasing number of multidrug resistant pathogens. Lipid A (endotoxin), the hydrophobic moiety of lipopolysaccharide (LPS), is a glucosamine-based saccharolipid that makes up the outer monolayer of the

outer membranes of most gram-negative bacteria [29]. It is the hydrophobic anchor of LPS and is essential for bacterial survival. There are approximately 10^6 lipid A residues in *Escherichia coli*. Thus, the biosynthesis of LPS (Figure 12) represents an attractive target for the development of novel antibiotics. LpxC catalyzes simple deacetylation of UDP-3-*O*-(*R*-3-hydroxymyristoyl)GlcNAc, the committed step in the biosynthesis of lipid A. This enzymatic reaction has been a major research focus for industrial groups and academic laboratories in the last two decades.
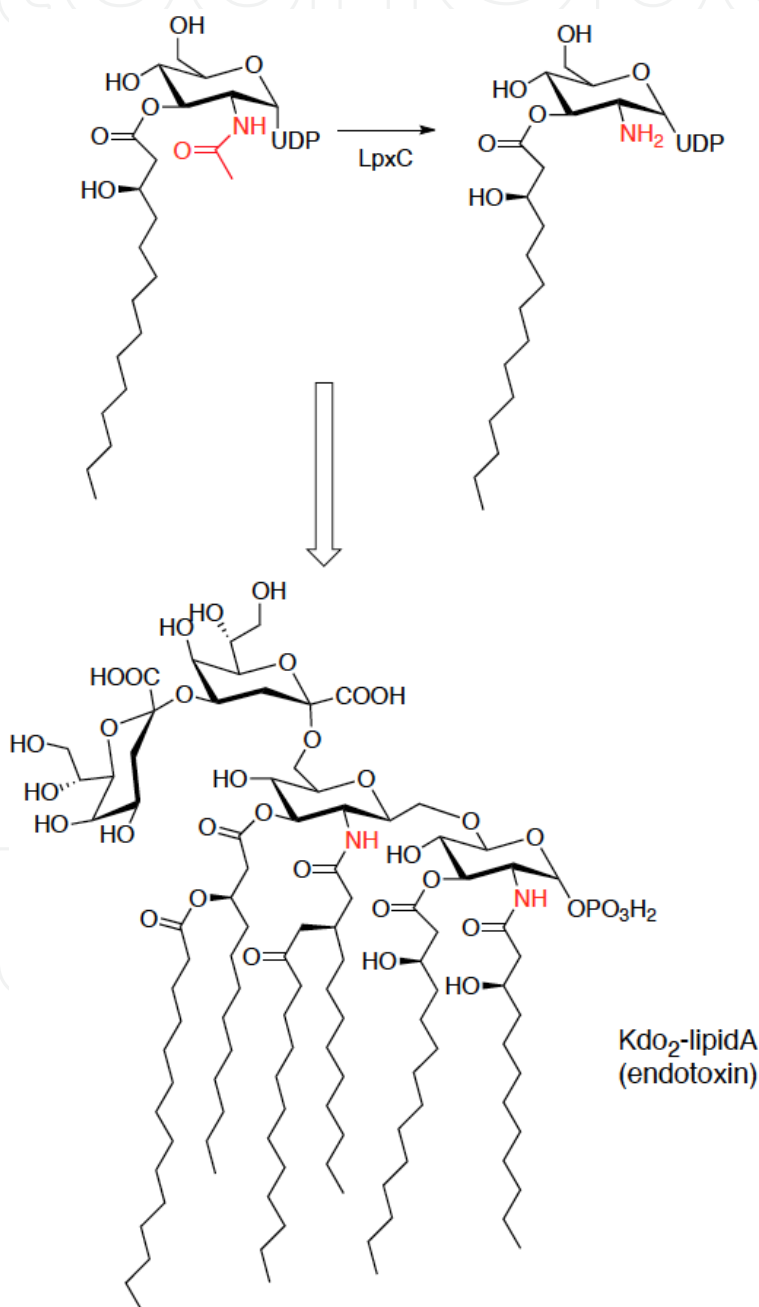
Figure 12. Lipid A biosynthetic pathway

Simple replacement of acetyl group of UDP-3-*O*-(*R*-3-hydroxymyristoyl)GlcNAc by hydroxamate moiety gave promising inhibitor of LpxC. Further reduction of its structure by removal of hydroxyl from hydroxymyristic acid (and thus removal of chiral center) followed by limiting the length of hydrophobic part of the molecule (Figure 13) afforded low-molecular inhibitor of LpxC (TU 519) shown in Figure 13. Such modifications were possible because lipidic part of the substrate is not bound by the enzyme and is freely exposed to the environment (Figure 13).
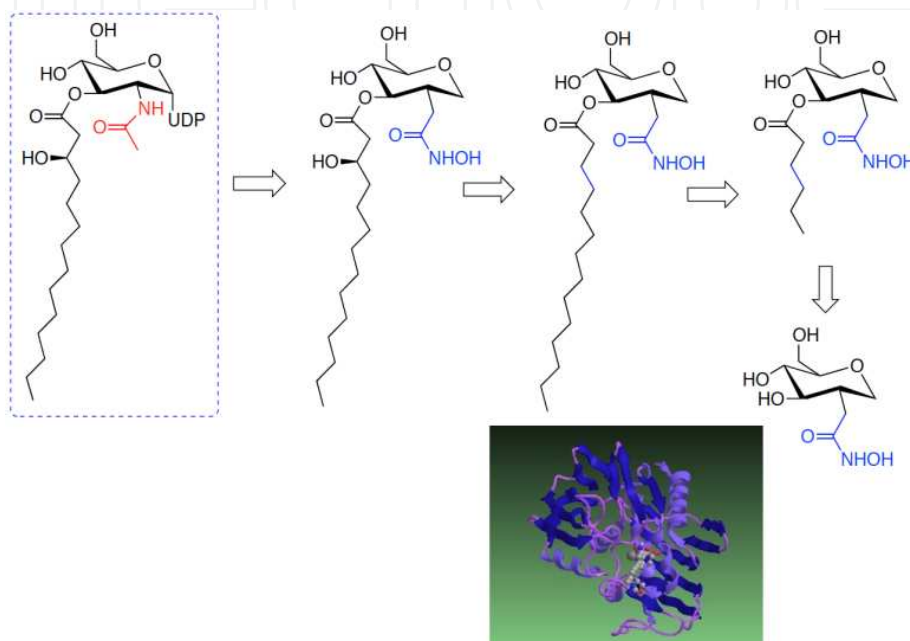

Figure 13. Stepwise reduction of lipidic part of LpxC inhibitor leading to TU 519 and explanation of the molecular basis of this process by X-ray structure of the enzyme bound with substrate

Further modifications of the structure of TU 519 molecule, enforced by analysis of crystal structures of enzyme-inhibitor complexes afforded nanomolar inhibitors of LpxC, however, none of them reached phase of clinical studies. Anyway, this approach is a good illustration that stepwise modifications of chemical structure of substrate afford inhibitors, structure of which is substantially different than parent one.

Neurotensin is a 13-amino acid peptide found in the central nervous system and the gastrointestinal tract. It has been shown to play the seemingly unrelated functions in the central nervous system and the periphery and thus is involved in a wide range of physiologic and pathologic processes throughout the body [29]. By selective targeting or blockade of specific neurotensin receptors potential drugs for use in the treatment of schizophrenia, alcoholism, chronic pain, or cancer have been found [30].

Meclinertant (SR-48692) is a drug, which acts as a selective, non-peptide antagonist of neurotensin receptor 1. It is used in research to explore the interaction between neurotensin and other neurotransmitters in the brain and is considered as potential anticancer agent [31]. Comparison of the modes of binding of neurotensin and SR-48692 indicates that they are

governed by the same interactions (Figure 15) and illustrates how far the structure of the drug differs from the structure of parent compound [32].
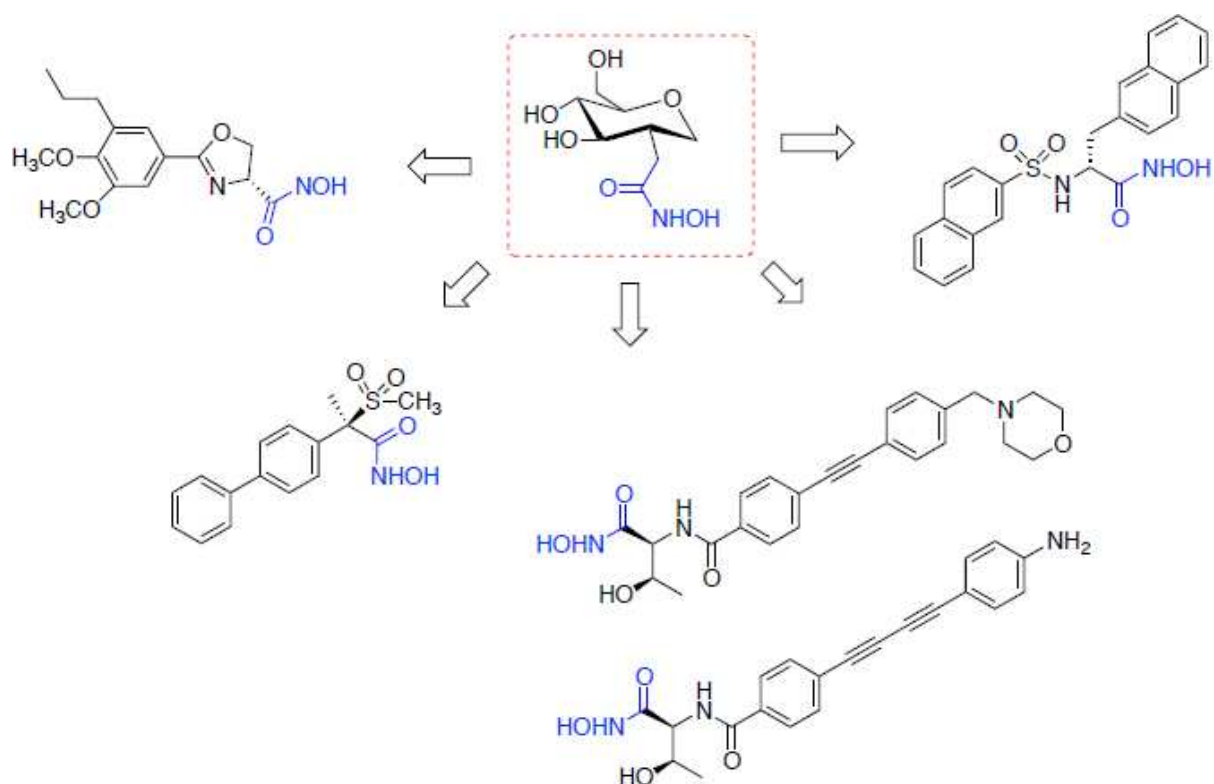
Figure 14. Inhibitors of LpxC obtained by stepwise modification of TU 519 structure
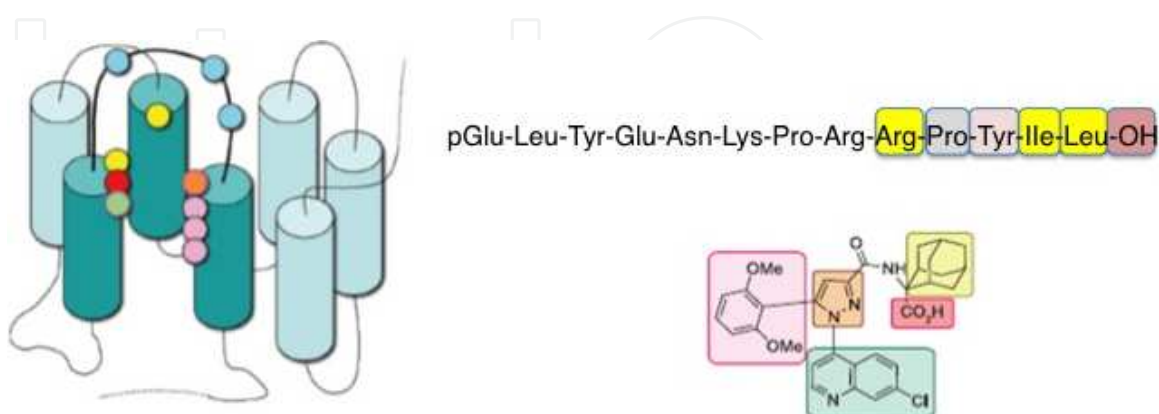
Figure 15. Binding of neurotensin and meclinertant to NRT1 receptor is governed by the same interactions. Amino acids of the receptor interacting with specific portions of effectors are represented by colored balls.

4. Mapping of structural preferences of binding sites of receptors of peptidyl hormones and enzyme inhibitors

Throughout the body, peptides are active regulators and information brokers with skill sets that make them interesting for drug discovery. The most commonly the search on peptide-like drugs is concentrated at discovery of agonists and antagonists of certain hormones and neuroregulators. On the other hand, short peptides, their analogues and mimetics are commonly applied as inhibitors of proteinases.

In order to introduce a peptide as a drug their low stability in body fluids and the fast clearance must be overcame. The simplest solution is replacement of terminal amino acids of lead compound by their enantiomers. This usually improves peptide hydrolytic stability, since enzymes do not hydrolyze peptide bond formed by *D*-amino acids.

Replacement of one or few amino acids of chosen hormone by their analogues is perhaps the oldest and most exploited technique for designing new drugs. Analogues of gonadotropin releasing hormone may serve as a good example here. This idea is well illustrated by comparison of the structures of four drugs with the structure with gonadotropin releasing hormone (GnRH) (Figure 16).

GnRH is the hypothalamic factor that mediates reproductive competence. This peptide composed of 10 amino acids triggers sexual development and it is essential for normal sexual physiology of both males and females [33]. In both sexes, its secretion occurs in periodic pulses usually occurring every 1–2 hours. GnRH secretion from the hypothalamus acts upon its receptor in the anterior pituitary to regulate the production and release of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH then stimulate sex steroid hormone synthesis and gametogenesis in the gonads. Therefore, analogues of GnRH are considered as drugs against sexual disorders [34].

Goserelin (*Zoladex*) obtained by modifications introduced at C-terminal glycine and serine-4 stops the production of sex hormones (testosterone and estrogen) and is used to treat hormone-sensitive cancers of the prostate and breast (in pre-/perimenopausal women) [35]. Cetrorelix (*Cetrotide*) obtained by modifications of GnRH chain in positions 1, 2, 3, 6 and 10 is a synthetic decapeptide with gonadotropin-releasing hormone antagonistic activity. It is used in assisted reproduction techniques to prevent premature LH surge in women undergoing controlled ovarian stimulation allowing the follicles to mature for planned oocyte collection [36].

Third analogue, Leuprolide (*Lupron, Leuprorelin*), which differs from parent hormone by modification of both glycines (positions 6 and 10), is used for the palliative treatment of advanced prostate cancer. In many cases, Lupron may slow or stop the growth of cancerous cells and relieve some of the associated symptoms [37]. Finally, Nafarelin (*Synarel*), which was obtained by replacement of glycine-6 by bulky aromatic non-proteinous amino acid, is used to relieve the symptoms of endometriosis, including menstrual cramps or low back pain during menstruation [38]. Synarel is also indicated for use in controlled ovarian stimulation programs prior to *in vitro* fertilization [39].
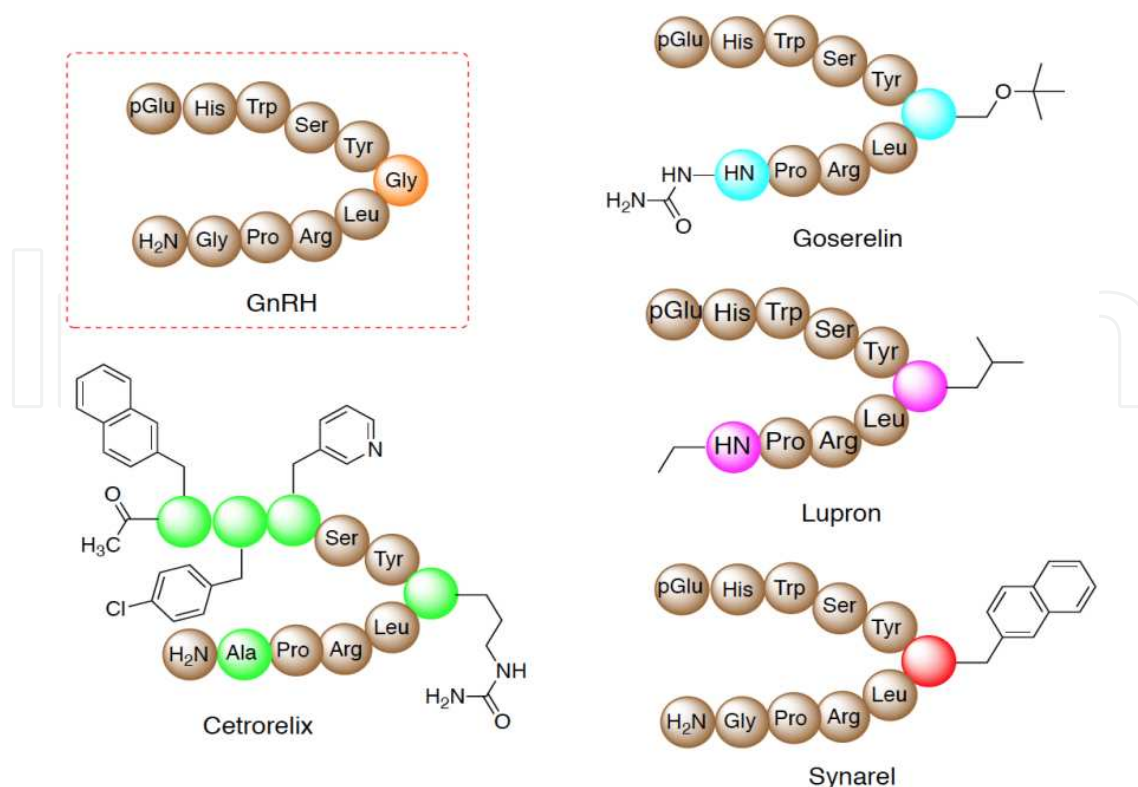
Figure 16. Comparison of structure of GnRH with its four analogues.

Of course, it is not possible to predict how the introduced change will reflect in certain activity. Therefore, cumbersome trials are needed to find out proper drug amongst thousands of synthesized analogues. It is worth to note that the replacement of each of ten amino acids in GnRH by 20 proteineous amino acids gives 10^{20} combinations. If considering that each natural amino acid could be replaced by many structurally different analogues (representative structures of analogues of phenylalanine are shown in Figure 17) not systematic approach but only luck may help to find interesting new drug. Therefore, application of combinatorial chemistry seems to be an obvious technique here [40].

The approach basing on substitution of amino acids surrounding active centers of proteinases is also applied for the design of peptidyl or peptidomimetic inhibitors of proteases. In this case, however, a new technique emerged, which is basing on screening of the activity of large libraries of fluorogenic substrates of chosen enzymes. This enables to determine substrate preferences of certain enzyme and thus to provide a set of data useful for the preparation of their selective inhibitors [41]. This approach, called enzyme profiling, was successfully used for differentiation of the binding requirements of the same enzymes isolated from different sources (orthologs) [42-44], which ensures that the inhibitors designed on the basis of this profiling would be species specific. The utility of this approach was validated by the preparation of potent inhibitors of M1 alanine aminopeptidase from *Neisseria meningitides* [45], a gram-negative diplococcus bacterium, which is the main causative agent of meningitis. It is the inflammation of the membranes lining the brain and spinal cord. This disease is particularly
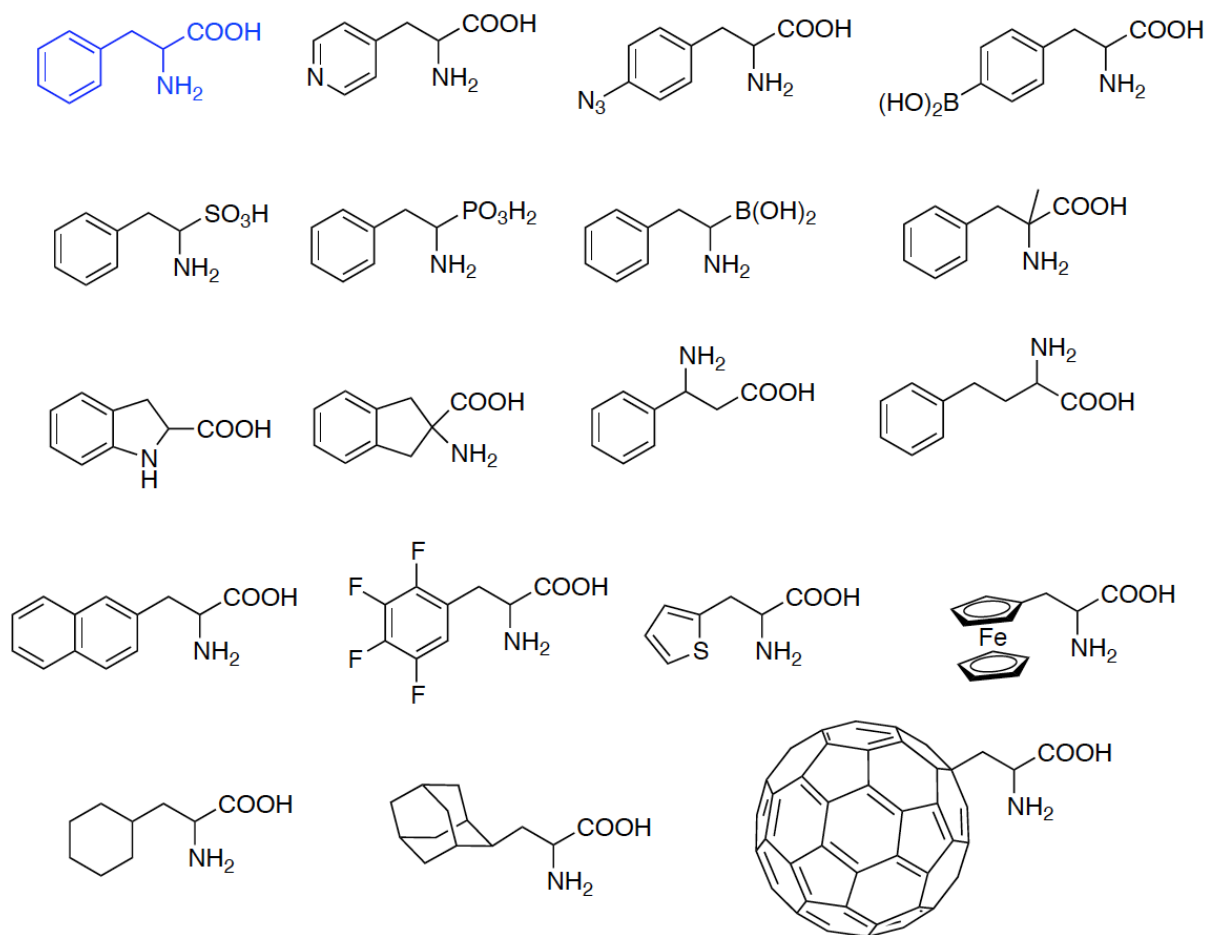
Figure 17. Representative variations of the structure of phenylalanine

dangerous as it can result in brain damage and eventually, if not treated promptly or left untreated, can lead to death. It mostly threatens children during the first year of life [45].

5. Inhibitors mimicking three-dimensional structure of active peptides and protein epitopes

It is well established that only several exposed amino acids of the hormone are responsible for physiologic effect. Therefore it is of interest to place their side chains in such a way that they ensure interaction with the appropriate receptor. Ocreotide (*Sandostatin*) is a drug elaborated basing on that concept. Somatostatin is a hormone that inhibits the secretion of several other hormones, including growth hormone, thyroid stimulating hormone, cholecystokinin and insulin. It has two active forms produced by alternative cleavage of a single preprotein: one of 14 amino acids, the other of 28 amino acids [46]. Ocreotide is an octapeptide, in which similar strain as in parent shorter hormone was introduced (Figure 18). It results in a similar exposition of phenylalanine, tryptophan, lysine and threonine. Additionally *D*-tryptophan and D-phenylalanine were applied to ensure higher hydrolytic stability of the drug. Ocreotide mimics

somatostatin pharmacologically, though it is a more potent inhibitor of growth hormone, glucagon, and insulin than the natural one. It is approved for the treatment of acromegaly, diarrhea and flushing episodes associated with carcinoid syndrome, and for the treatment of diarrhea in patients with vasoactive intestinal peptide-secreting tumors [47]. Lanreotide (*Somatuline*) is a simple analogue of Ocreotide in which C-terminal threoninol was replaced by threonine amide (Figure 18) [48]. It is also approved as a drug against acromegaly, a hormonal disorder that results when the pituitary gland produces excess growth hormone (GH). It most commonly affects middle-aged adults and can result in serious illness and premature death.
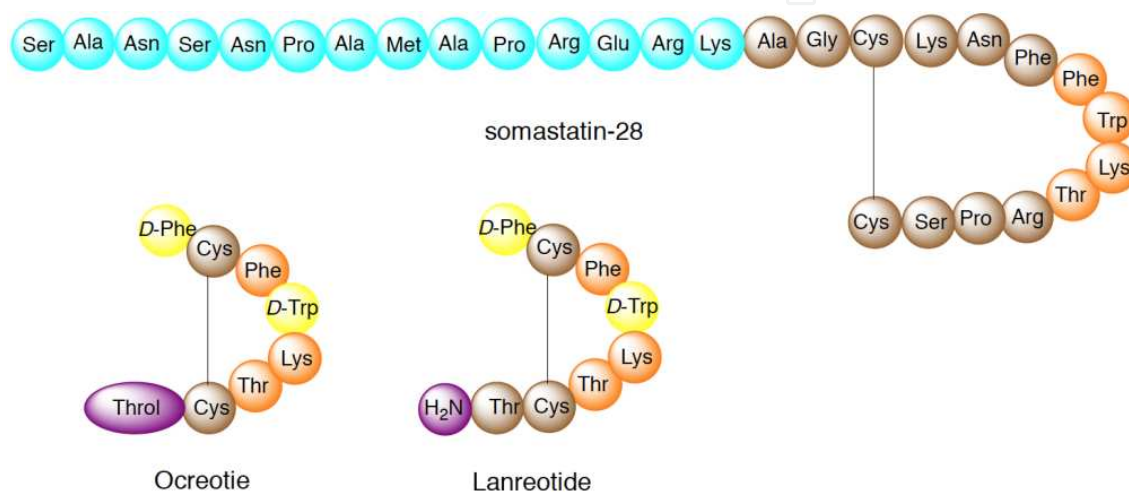
**Figure 18.** Somatostatin and its analogues: Ocreotide and Lanreotide

The next generation of analogues started with discovery of Ocreotide structural analogue, L-363,301 hexapeptide (Figure 19) bearing properly exposed side chains of phenylalanine, tryptophan, lysine and threonine and displaying high biological activity in inhibiting the release of growth hormone, insulin, and glucagon [49]. Quite interestingly N-methylation of tryptophan, lysine and phenylalanine of this peptide resulted in its elevated oral bioavailability [50]. This finding served as inspiration for the development of somatostatin analogues, in which the side-chains of four amino acids responsible for physiologic effect are placed on cyclic scaffolds. The representative examples of compounds obtained by this approach are shown in Figure 19 and include: a backbone-cyclic somatostatin analogue PTR 3046 [51], a selective agonist of one out of five receptors (SSTR5 receptor); tetrapeptide composed of four β-amino acids [52]; *N*-peptoid analog of the cyclo β-peptide of low micromolar affinity but strong selectivity towards SSTR5 receptor [53] and somatostatin mimetic, based on the *D*-glucose scaffold considered as the landmark on this field [54]. Unfortunately none of these compounds have found an application in medicine, however, discovery of Pasireotide (*Signifor*) (Figure 19) is an example of successful implementation of this strategy. Pasireotide is an orphan drug approved in U.S.A. and Europe for the treatment of Cushing's disease in patients who fail or are in ineligible for surgical therapy [55].
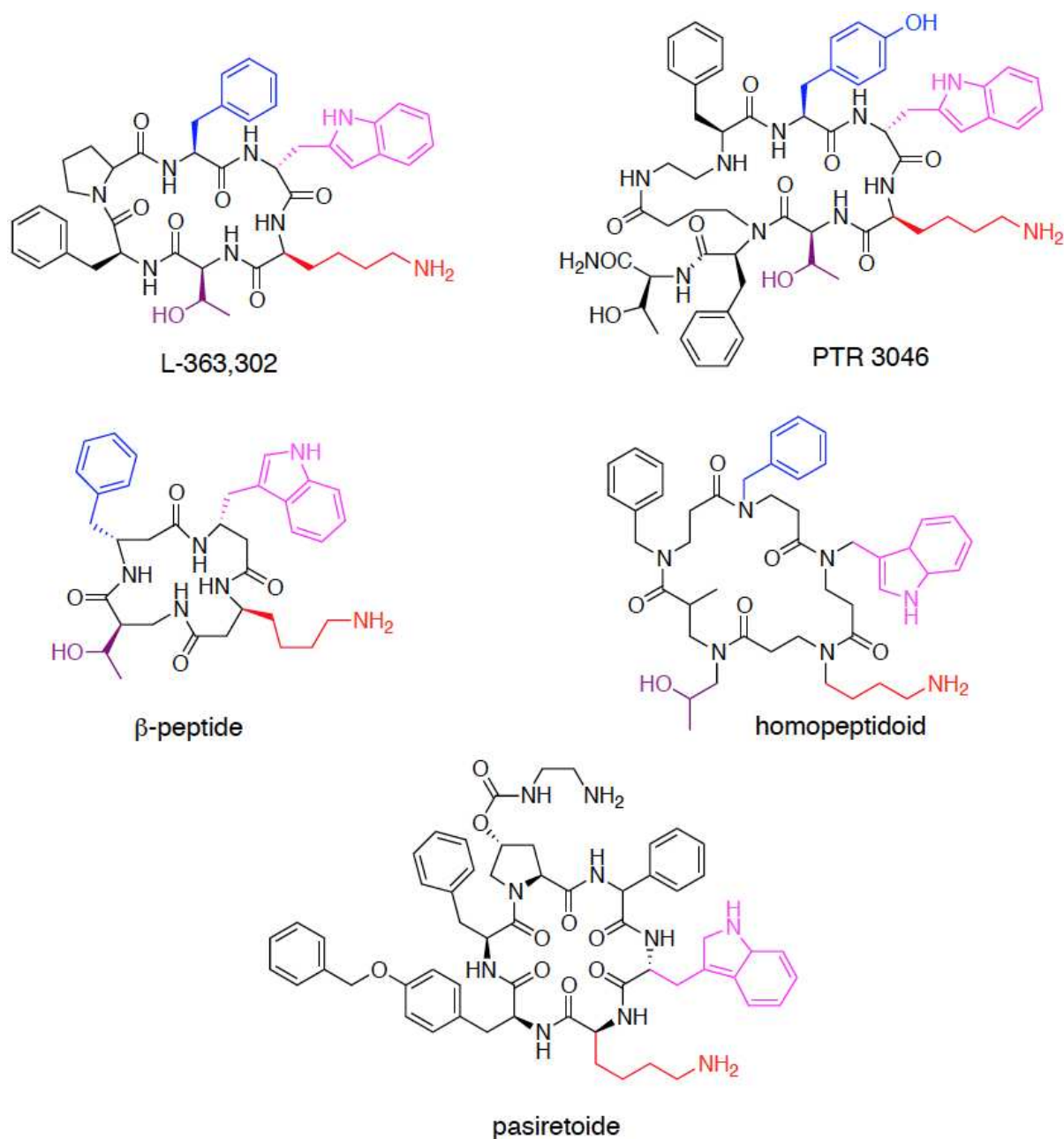
Figure 19. Analogues of somatostatin built-up on cyclic scaffolds

Similar approach was used for design antagonists and agonists of γ-agatoxin IVB. It is one of the toxins extracted from American funnel web spider *Agelenopsis aperta.* This 48 amino acid protein is a very selective antagonist of the P-type calcium channels. Because γ-agatoxin IV docks to the channel protein via loop composed of eight amino acids, which are located between the 11 and 18 amino acids, this fragment was chosen to find the minimal sequence, which possesses the activity of calcium channel modulators. Therefore, constrained cyclic analogues with three-dimensional arrangement corresponding to the native structure of the loop were designed (Figure 20). The neurophysiological experiments confirmed the proper choice of the mimetics and the necessity of the presence of properly directed tryptophan (an

amino acid fundamental for activity) residue for toxin-channel interactions [56,57]. The synthesized agonists might be useful for the development of treatment for patients with calcium like migraine, related to decreased calcium influx.
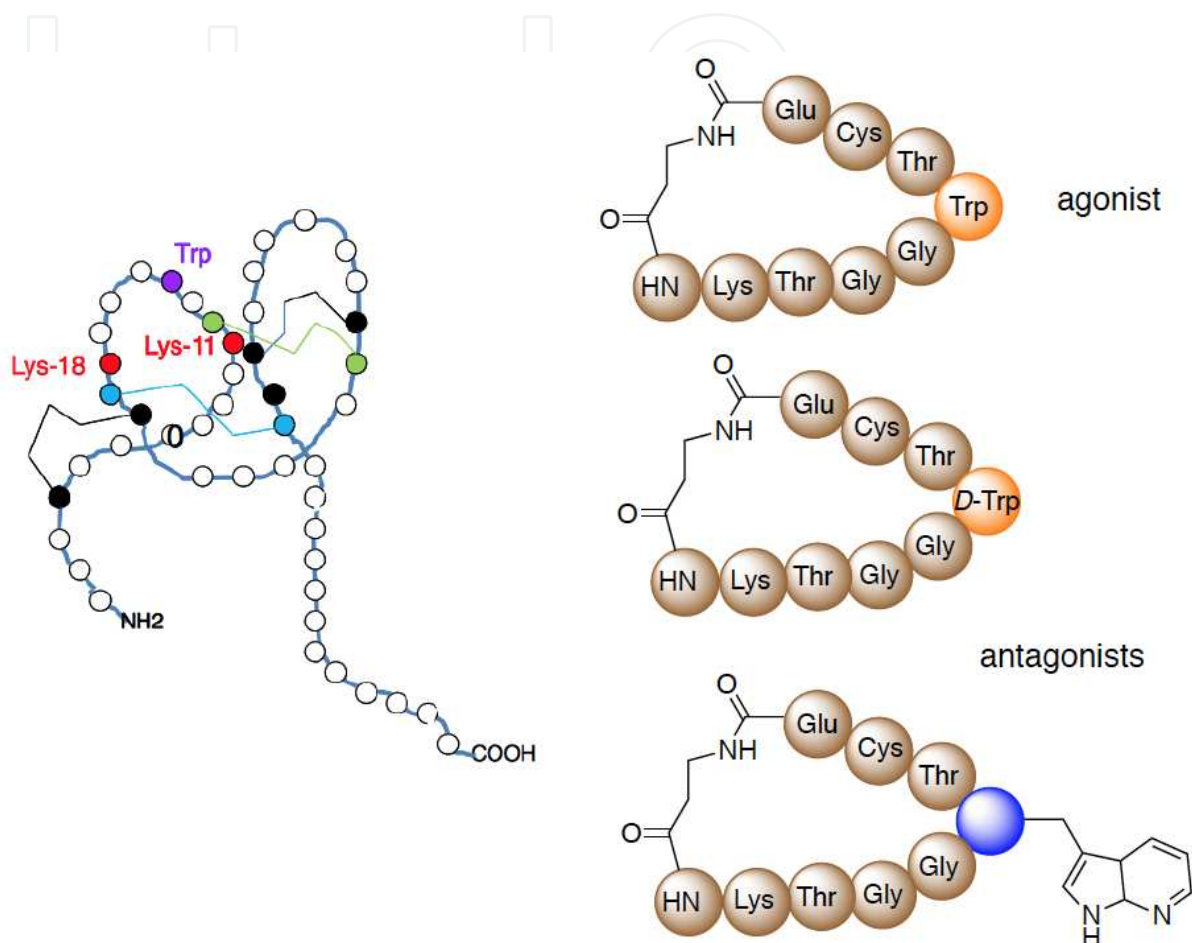
Figure 20. Structure of γ-agatoxin IVB and two of its simplified analogues.

Human immunodeficiency virus (HIV) entry is a complex and intricate process that facilitates delivery of the viral genome to the host cell. For entry to occur the outer viral envelope protein gp120 sequentially engages the host protein CD4. The exact mechanism by which the virus enters the cell is not known in detail; however, it is known that gp120 plays a critical role here [58]. Its role is to seek receptors suitable for viral entry and to fix the viral particle to the cell. Since gp120 is trimeric, trivalent synthetic miniproteins CD4M9 (analogues of scorpio scylla-toxin) [59], mimicking DC4 receptor, were designed to target the CD4-binding sites displayed in the trimeric gp120 complex of HIV-1 (Figure 21). These miniproteins bound via thiol moieties to symmetrical scaffolds demonstrated significantly enhanced anti-HIV activities over the monomeric ones [60].
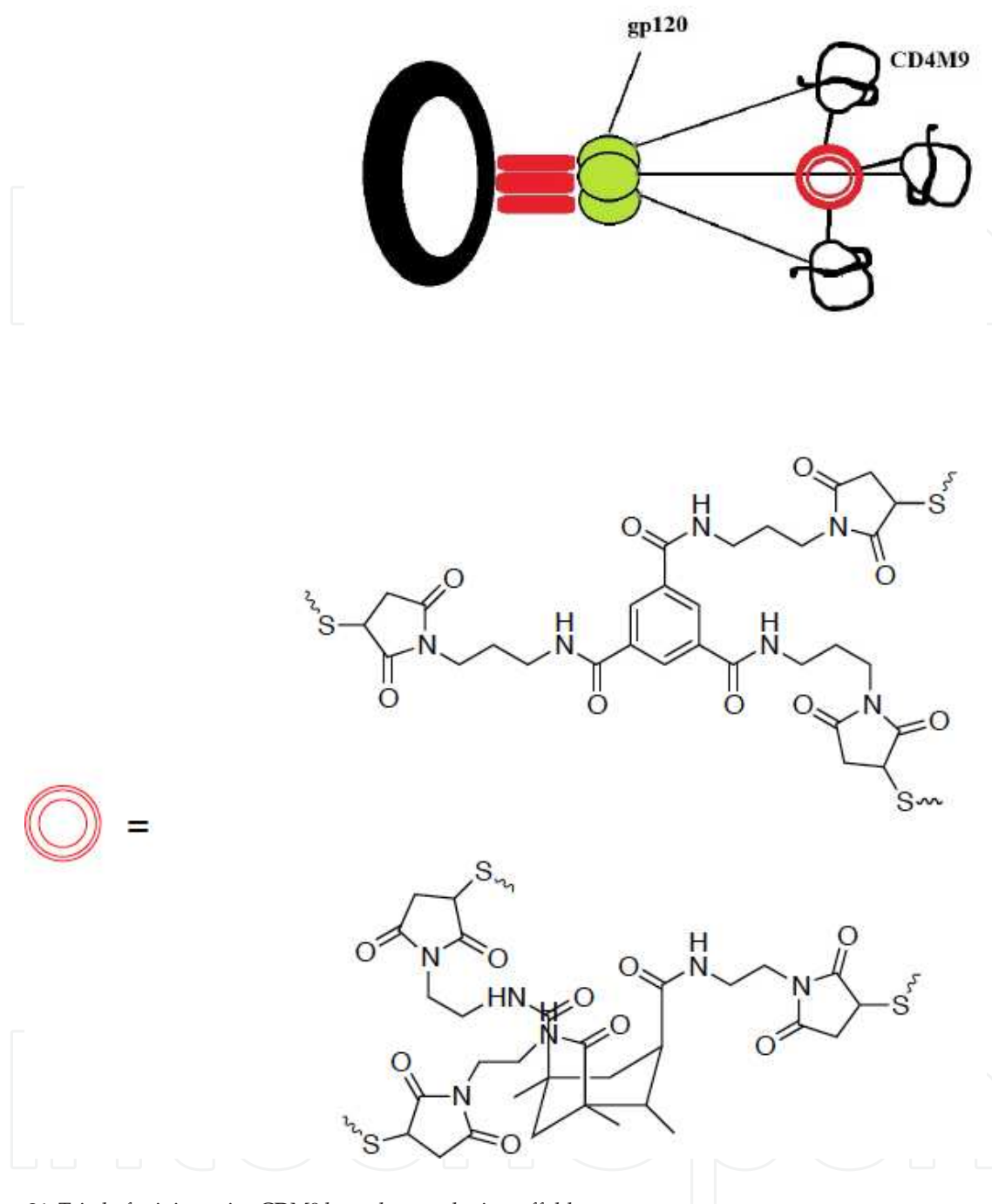
Figure 21. Triad of miniproteins CDM9 bound to synthetic scaffolds

6. Topographical complementarity as a mean for inhibitor design

Human hormone effectors such as: meclinertant (neurotensin receptor, Figure 13), ezlopitant (neurokinin receptor) [61], CP-154,526 (corticotropin-releasing hormone receptor) [62], SM-130,686 (growth hormone secretatogue) [63], asperlicin (cholecysatokinin receptor) [64] or galantanamine (nicotinic receptor) [65], have been discovered either by serendipity or were

isolated from natural sources. Their structures are significantly different from natural hor-
mones (Figure 22) and therefore it is very difficult to design drugs basing on binding modes
of these hormones with their receptors.
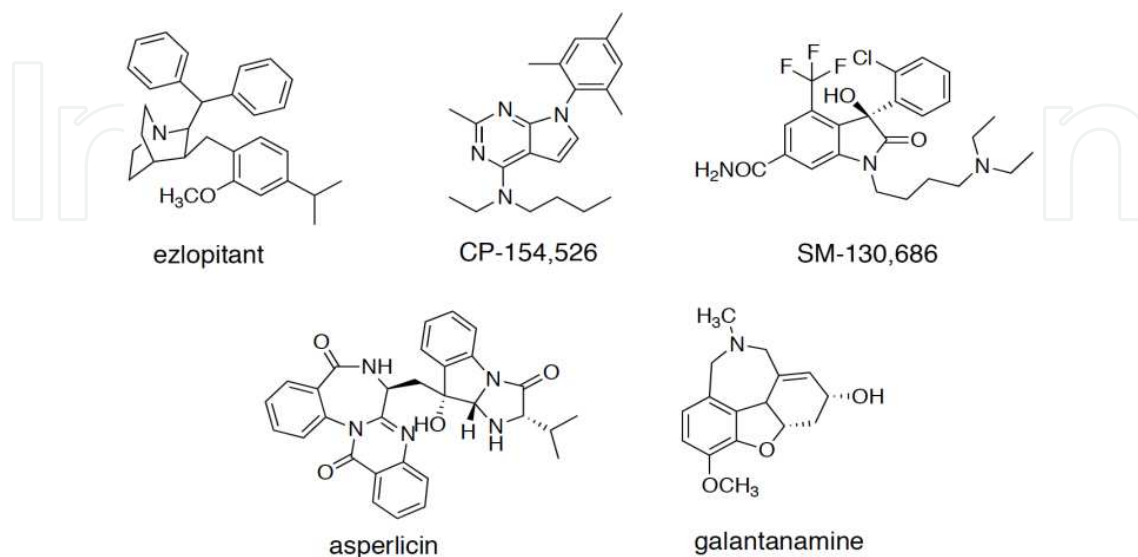
Figure 22. Structures of chosen effectors of hormone receptors

Although today it is not possible to design rationally new drugs of this kind, some hope is
brought with development computer-aided methods. The search for compounds with similar
activity to the reference ligand but with different molecular frameworks have been named
"scaffold hopping" or "leapfrogging" [66]. It basically relays on three-dimensional similarity
searching. However, an adequate description of chemical structures in 3D conformational
space is difficult due to the high-dimensionality of the problem and this methodology might
be considered as being in its infancy so far [67].

Other solution is the application of peptidomimetics. They derive from natural peptides and
proteins and are obtained by structural modifications using unnatural amino acids, replace-
ment of peptide bond by appropriate surrogates or introduction of conformational restrains.
Peptidomimetics represent an important field in chemistry as they circumvent the limitations
of traditional peptides used in therapy. Self-structural organizations such as turns, helices,
sheets and loops can be accessed by this way [68,69].

Antimicrobial peptides are an important component of the natural defense of most living
organisms against invading pathogens. These are relatively small, cationic and amphipathic
peptides of variable length, sequence and structure. Magainins are a class of antibacterial
peptides isolated from the surface of skin of African clawed frog *Xenopus laevis* [70]. They
disrupt only the bacterial membranes possibly via toroidal-type pore formation and have
minimal interaction with the mammalian cell membranes. It is believed that the structure of
the magainins-in particular a long, repeating helix-is important to their bactericidal activities.
Although strongly active in vitro, are effective in animal models of infection only at very high
doses, often close to the toxic ones, reflecting an unacceptable margin of safety.

A series of peptides composed of only two strained β-amino acids (Figure 23) were designed in order to posses helical structure and display required optimal amount of cationic residues versus hydrophobic ones (in ratio 4:6) at the helical surface. They appeared to be strongly antibacterial and act in a similar manner as magainins. Moreover, they appear to lack hemolytic activity and are resistant to action of proteinases, which are the major drawbacks of the parent compounds [71,72]. Similar, although less spectacular, effect was obtained with oligo-β-peptides obtained using analogues of natural amino acids [73].
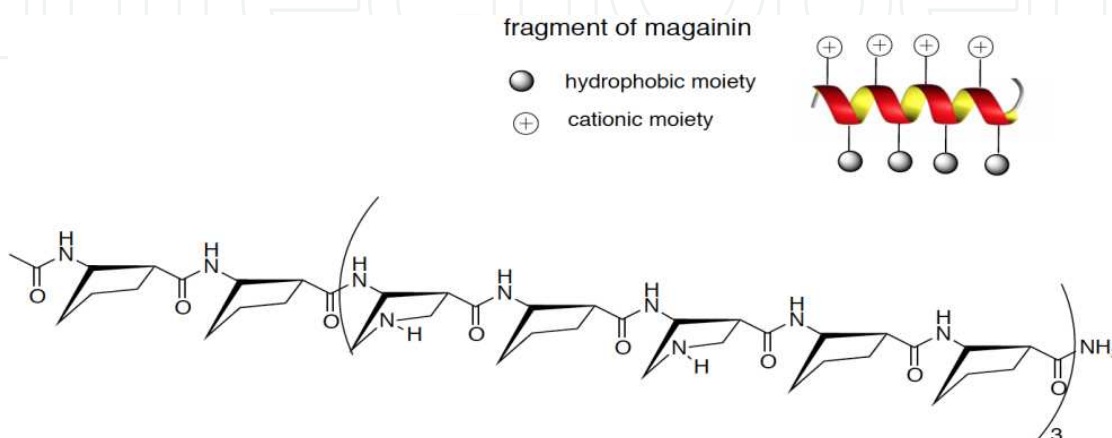

Figure 23. Amphiphilic structure of magainin and its topographical analog

N-Substituted poly(glycines), called peptidoids, are another subclass of peptidomimetics. Such oligomers, mimicking magainins, with facially amphipathic, cationic, water-soluble sequences have also been shown to form very stable helices and exhibit antibacterial properties [74].

The findings that nonhelical analogues are nonetheless active against bacterial pathogens encouraged to further simplify search for new magainin mimetics and pursue alternative design concepts. Application of poly(arylamides) appears to be successful. The structure of these molecules is shown in (Figure 24) and indicates that their backbone design has nothing in common with parent compounds. They have a rigid backbone made from amide-linked aromatic repeat units, which are further stabilized by hydrogen bonding between a thioester and the hydrogen on an amide group. This locks the pendant hydrophobic *t*-butyl groups and the hydrophilic ammoniums group on opposite sides of the molecule as it is in the case of magainins (Figure 24). It was shown that such foldamers were active against a number of gram-positive and gram-negative bacterial strains [75,76]. This finding stimulates an intensive research on polymeric mimicks of magainins and shows that topographical similarity has not to be very strict [77].

The described above topographical approach have been also used to produce mimetics of enzymes, hormones [77] and lung surfactants [78,79]. Lung surfactants are a complex mixture over 50 lipid species lining the alveolar air-liquid interface. They are indispensable for proper functioning of the lungs and their absence or dysfunction leads to severe respiratory disease. The application of exogenous lung surfactants to treat neonatal distress syndrome dramatically
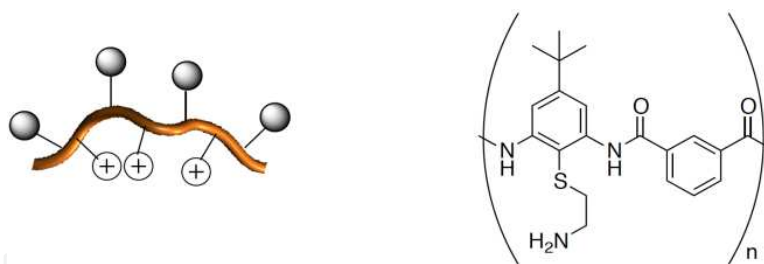
Figure 24. Poly(arylamides) mimicking the structure of magainins

improved premature infant survival and respiratory morbidity [80]. The possible application of their stable analogues is considered as a next step in curing this disease.

7. Conclusions

Analogy plays an important role in scientific research. Analogue-based approach of drug design is one of the oldest methodologies of medicinal chemistry and still is intensively exploited one. It started from production of antimetabolites by simple replacement of small functional groups in physiologically important molecules by isosteric and isoelectronic substituents. The development of biochemistry and pharmacology resulted in search for substances mimicking three-dimensional architecture of biologically active substances rather than seeking for simple analogues. Enforced by new techniques, such as combinatorial chemistry and computer-aided drug design, structural analogy is a reach source of new substances of potential medical importance.

Author details

Paweł Kafarski[1,2*] and Magdalena Lipok[2]

*Address all correspondence to: pawel.kafarski@pwr.edu.pl

1 Faculty of Chemistry, Wrocław University of Technology, Wrocław, Poland

2 Faculty of Chemistry, Opole University, Opole, Poland

References

[1] Bosch R, Roisch L. The Contributions of Paul Ehrlich to Pharmacology: A Tribute on the Occasion of the Centenary of His Nobel Prize. Pharmacology 2008; 82(3) 171-179; doi:10.1159/000149583

[2]   Lloyd NC, Morgan HW, Nicholson BK, Ronimus RS, Riethmiller S. The Composition of Ehrlich's Salvarsan: Resolution of a Century-Old Debate. Angewandte für Chemie International Edition 2005; 44(6) 941-944

[3]   Bakston J, Gerhard Domagk and the Discovery of Sulfa Drugs. Hockessin: Mitchell Lane Publishers; 2003

[4]   Bentlet R. Different Roads to Discovery; Prontosil (hence Sulfa Drugs) and Penicillin (hence beta-Lactams). Journnal of Industrial Microbiology 2009; 36(6) 776-786; doi: 10.1007/s10295-009-0553-8

[5]   Chan ESL, Cronstein BN. Methotrexate – Hoe Doas It Really Work? Nature Reviews Reumathology 2010: 6(3) 175-178; doi:10.1038/nrrheum.2010.5

[6]   DeRuiter J. Narcotic Analgesics: Morphine and "Periferally Modified" Morphine Analogs. Principles of Drug Action. Fall 2000. http://www.lopdf.net/

[7]   Froestl W, Mickel SJ, Hall RG, von Sprecher G, Strub D, Baumann PA, Brugger F, Gentsch C, Jaekel J, Olpe HR, Rihs G, Vassout A, Waldmeier PC, Bittiger H. Phosphinic Acid Analogs of GABA. 1. New Potent and Selective GABAB Agonists. Journal of Medicinal Chemistry 1995; 38(17) 3297-3312: doi:10.1021/jm00017a015

[8]   Messaoudi S, Peyrat JF, Brion JD, Alami M. Heat-Shock Protein 90 Inhibitors as Antitumor Agents: a Survey of the Literature from 2005 to 2010. Expertr Opinion on Therapeutic Patents 2011; 21(10) 1501-1542; doi:10.1517/13543776.2011.594041.

[9]   Bender DM, Peterson JA, McCarthy JR, Gunaydin H, Takano Y, Houk KN. Cyclopropanecarboxylic Acid Esters as Potential Prodrugs with Enhanced Hydrolytic Stability. Organic Letters 2008; 10(3) 509-511; doi:10.1021/ol702892e

[10] Kubinyi H. Chemical Similarity and Biological Activities. Journal of Brazylian Chemical Society 2002; 13(6) 717-726; doi: org/10.1590/S0103-50532002000600002

[11] Petrone P, Simms B, Nigsch F, Lounkine E, Kutchukian P, Kornett A, Dedng Z, Davies JW, Jenkins JL, Glick M. Rethinking Molecular Similarity: Comparing the Compounds on Basis of Biological Activity. ACS Chemical Biology 2012; 7(8); doi:10.1021/cb3001028

[12] Geysen HM, Schoenen F, Wagner D, Wagner R. Combinatorial Compound Libraries for Drug Discovery: an Ongoing Challenge. Nature Reviews. Drug Discovery. 2003; 2(3) 222-230; doi:10.1038/nrd1035

[13] Gupta SP., Matrix Matalloprotease Inhibitors. Specificity of Binding and Structure-Activity Relationship. Basel; Springer; 2012

[14] Brown S, Meroueh SO, Fridman R, Mobashery S. Quest for Selectivity in Inhibition of Matrix Metalloproteinases. Current Topics in Medicinal Chemistry 2004; 4(12) 1227-1238; doi:org/10.2174/1568026043387854

[15] Yiotakis A, Dive V. Synthetic Active Site-directed Inhibitors of Metzincins: Achievement and Perspectives. Molecular Aspects of Medicine 2008; 29(5) 329-338; doi: 10.1016/j.mam.2008.06.001

[16] Devel L, Rogakos V, Arnaud D, Makaritis A, Beau F, Cuniasse F, Yiotakis A, Dive V. Development of Selective Inhibitors and Substrate of Matrix Metalloproteinase-12. Journal of Biological Chemistry 2006; 281(16) 11152-11160; doi:10.1074/jbc.M600222200

[17] Berlicki Ł, Grembecka J, Dyguda-Kazimierowicz E, Kafarski P, Sokalski WA. From Inhibitors of LAP to Inhibitors of PAL. Lessons from Molecular Interface and Experimental Interface. In: Sokalski WA (ed.) Molecular Materials with Specific Interactions – Modeling and Design Challenges and Advances in Computational Chemistry and Physics Series IV. Dordrecht: Springer 2006 p365-398.

[18] Dheda K, Gumbo T, Gandhi NR, Murray M, Theron G, Udwadia Z, Migliori GB, Warren R. Global Control of Tuberculosis: from Extensively Drug-resistant to Untreatable Tuberculosis. The Lancet Respiratory Medicine 2014; 2(4) 321-338; doi: 10.1016/S2213-2600(14)70031-1

[19] Berlicki Ł. Inhibitors of Glutamine Synthetase and their Potential Application in Medicine. Mini-Reviews in Medicinal Chemistry 2008; 8(9), 1-10; doi: 10.2174/138955708785132800

[20] Eisenberg D, Gill HS, Pfluegl GMU, Rotstein SH. Structure-function Relationships of Glutamine Synthetases. Biochimica et Biophysica Acta. 2000; 1477(1-2) 122-145; doi: 10.1016/S0167-4838(99)00270-8

[21] Böhm HJ. The Computer Program LUDI: a New Method for the de novo Design of Enzyme Inhibitors. Journal of Computer-Aided Molecular Design 1992; 6(1) 61-78; doi:10.1007/BF00124387

[22] Berlicki Ł, Obojska A, Forlani G, Kafarski P. Design, Synthesis, and Activity of Analogues of Phosphinothricin as Inhibitors of Glutamine Synthetase. Journal of Medicinal Chemistry 2005; 48(20) 6340-6349; doi:10.1021/jm050474e

[23] Huennekens FM. The Methotrexate Story: A Paradigm for Development of Cancer Chemotherapeutic Agents. Advances in Enzyme Regulation 1994; 34 397-419; doi: 10.1016/0065-2571(94)90025-6

[24] Dhar H, Hamdi I, Rathi B. Methotrexate Treatment of Ectopic Pregnancy: Experience at Nizwa Hospital with Literature Review. Oman Medical Journal 2011; 26(2) 94-98; doi:10.5001/omj.2011.24

[25] Longo-Sorbello GSA, Bertini JR. Current Understanding of Methotrexate Pharmacology and Efficacy in Acute Leukemias. Use of Newer Antifolates in Clinical Trials. Haematologica 2001; 86(2) 121-127;

[26] Norris RE, Adamson PC. Clinical Potency of Methotrexate, Aminopterin, Talotrexin and Pemetrexed in Childhood Leukemias. Cancer Chemitherapy and Pharmacology 2010; 65() 11250-1130; doi:10.1007/s00280-009-1120-8

[27] Kline CLB, El-Deiry WS. Personalizing Colon Cancer Therapeutics: Targeting Old and New Mechanisms of Action. Molecules 2013; 6(8) 988-1038; doi:10.3390/ph6080988

[28] Delfino RT, Santos-Filho OA, Figueroa-Villar JD. Type 2 Antifolates in the Chemotherapy of *falciparum* Malaria. Journal of Brazilian Chemical Society 2002; 13(6) 727-741; doi: org/10.1590/S0103-50532002000600003

[29] Mustain WC, Rychachou PG, Evers BM. The Role of Neurotensin in Physiologic and Pathologic Processes. Current Opinion in Endocrinology, Diabetes and Obesity 2011; 18(1) 75-82; doi:10.1097/MED.0b013e3283419052

[30] McMahon BM, Boules M, Warrington L, Richelson E. Neurotensin Analogs Indications for Use as Potential Antipsychoic Agents. Life Science 2002; 70(10) 1101-1119; doi:10.1016/S0024-3205(01)01520-X

[31] Baxendale IR, Cheung S, Kitching MO, Ley SV, Shearman JW. The Synthesis of Neurotensin Anragonist SR 48692 for Prostate Cancer Research. Bioorganic and Medicinal Chemistry 2013; 21(14) 4378-4387; doi:10.1016/j.bmc.2013.04.075

[32] Myers MM, Shearman JW., Kitching MO, Ramos-Montoya A, Neal DA, Ley SW. Cancer, Chemistry, and the Cell: Molecules that Interact with the Neurotensin Receptors. ACS Chemical Biology 2009 4(7) 503-525; doi:10.1021/cb900038e

[33] Schneider F, Gomek W, Gründker C. Gonadotropin-releasing Hormone (GnRH) and Its Natural Aalogues: a Review. Theriogenology 2006; 66(4) 691-709; doi:10.1016/j.theriogenology.2006.03.025

[34] Hayden C. GnRH Analogues: Applications in Assisted Reproductive Techniques. European Journal of Endocrinology 2008; 159(Suppl.1) S17-S25; doi:10.1530/EJE-08-0354

[35] Cheer SM, Plosker GL, Simpson D, Wagstaff AJ. Goserelin: A Review of its Use in the Treatment of Early Breast Cancer in Premenopausal and Perimenopausal Women. Drugs 2005; 65(18) 2639-2655; doi:10.2165/00003495-200565180-00011

[36] Reissmann T, Schally AV, Bouchard P, Riethmüller H, Engel J. The LHRH Antagonist Cetrorelix: A Review. Human Reproduction Update 2000; 6(4) 322-331; doi:10.1093/humupd/6.4.322

[37] Plosker GL, Brogden RN. Leuprorelin. A Review of Its Pharmacology and Therapeutic Use in Prostatic Cancer, Endometriosis and Other Sex Hormone-related Disorders. Drugs 48(6) 930—967; doi:10.2165/00003495-199448060-00008

[38] Chrisp P. Nafarelin. A review of its pharmacodynamic and pharmacokinetic properties, and clinical potential in sex hormone-related conditions. Drugs 1990; 39(4) 523-551; doi: 10.2165/00003495-199039040-00005

[39] Wong JM, Forrest KA, Snabes MC, Zhao SZ, Gersh G, Kennedy SH. Efficiacy of Nafarelin in Assisted Reproductive Technology: A Meta-Analysis. Human Reproduction Update 2001; 7(1) 92-10.

[40] Hruby VJ. *Designing Peptide Receptor Agonists and Antagonists. Nature Reviews. Drug Discovery* 2002; 1(11) 847-858; doi:10.1038/nrd939

[41] Drąg M, Salvesen GS, Emerging Principles in Protease-based Drug Discovery. Nature Reviews. Drug Discovery 2010; 9(9) 690 – 701; doi:10.1038/nrd3053

[42] Poręba M, McGowan S, Skinner-Adams TS, Trenholme KR, Gardiner DL, Whisstock JC, To J, Salvesen GS, Dalton JP, Drąg M. Fingerprinting the Substrate Specificity of M1 and M17 Aminopeptidases of Human Malaria, *Plasmodium Falciparum*. PLoS One 2012, 7(2) 31938; doi:10.1371/journl.pone.0031938

[43] Kasperkiewicz P, Poręba M, Snipas SJ, Parker H, Winterbourn CC, Salvesen GS, Drąg M. Design of Ultrasensitive Probes for Human Neutrophil Elastase through Hybrid Combinatorial Substrate Library Profiling. Pro cedings of National Academy of Sciences of U. S. A. 2014, 111(7) 2518 – 2523; doi:10.1073/pnas.13128548111

[44] Poręba M, Mihelic M, Krai P, Rajkovic J, Krężel A, Pawełczak M, Klemba M, Turk D, Turk B, Latajka R, Drąg M. Unnatural Amino Acids Increase Activity and Specificity of Synthetic Substrates for Human and Malarial Cathepsin C. Amino Acids 2014, 46(4) 931 – 943; doi:10.1007/s00726-013-1654-2

[45] Węglarz-Tomczak E, Poręba M, Byzia A, Berlicki Ł, Nocek B, Mulligan R, Joachimiak A, Drąg M, Mucha A. An Integrated Approach to the Ligand Binding Specificity of *Neisseria meningitidis* M1 Alanine Aminopeptidase by Fluorogenic Substrate Profiling, Inhibitory Studies and Molecular Modeling. Biochimie 2013, 95(2) 419 – 428; doi: 10.1016/j.biochi.2012.120.018

[46] Eigler T, Ben-Shlomo A. Somatostatin System: Molecular Mechanisms Regulating Anterior Pituitary Gland. Journal of Molecular Endocrinology 2014; 53(1) R1–R19; doi: 10.1530/JME-14-0034

[47] Lamberts SWJP van der Lely A-P, de Herder WW, Hofland LJ. Ocreotide. The New England Journal of Medicine 1996; 334(1) 246-254; doi:10.1056/NEJM199601253340408

[48] Croxtall JD, Scott JL. Lanreotide Autogel: A Review of Its Use in the Management of Acromegaly. Drugs 2008; 68(5) 711-723; doi:10.2165/00003495-200868050-00013

[49] Veber DF, Holly FW, Palaveda WJ, Nutt RF, Bergstand SJ, Torchiana M, Glitzer MS, Saperstein R, Hirschmann RF. Conformationally Restricted Bicyclic Analogs of Somatostatin. Proceedings of National Academy of Sciences of U.S.A. 1978: 75(6) 2636-2640.

[50] Biron E, Chatterjee J, Ovadia O, Langenegger D, Brueggen J, Hoyer D, Schmidt HA, Jelinek R, Gilon C, Hoffman A, Kessler H. Improving Oral Bioavailability of Peptides by Multiple N-Methylation: Somatostatin Analogues. Angewandte für Chemie (International Edition in English) 2008; 47(14) 2595-2599; doi:10.1002/anie.200705797

[51] Gilon C, Huenges M, Mathä B, Gellerman G, Hornik V, Afargan M, Amitay O, Ziv O, Feller E, Gamliel A, Shohat D, Wanger M, Arad O, Kessler H. A Backbone-cyclic, Receptor 5-selective Somatostatin Analogue: Synthesis, Bioactivity, and Nuclear Magnetic Resonance Conformational Analysis. Journal of Medicinal Chemistry 1998; 41(6) 919-929; doi:10.1021/jm970633x

[52] Seebach D, Gardiner J. β-Peptidic peptidomimetics, Accounts of Chemical Research 2008; 41(10) 1366-1375; doi:10.1021/ar700263g

[53] Seebach D, Schaeffer L, Brenner M, Hoyer D. Design and Synthesis of β-Dipeptide Derivatives with Submicromolar Affinities for Human Somatostatin Receptors. Angewandte für Chemie (International Edition in English) 2003; 42(7) 776-778; doi: 10.1002/anie.200390205

[54] Hirschmann RF, Nicolaou KC, Angeles AR, Chen JS, Smith III AB. The β-D-Glucose Scaffold as a β-Turn Mimetic. Accounts of Chemical Research 2009; 42(10) 1511-1520; doi:10.1021/ar900020x

[55] Feelders RA, Yasothan U, Kirkpatrick P. *Pasireotide. Nature Reviews. Drug Discovery* 2012; 11(8) 597-598; doi:10.1038/nrd3788

[56] Minta E, Kafarski P, Martinez J, Rolland V. Synthesis of Cyclooctapeptides: Constraints Analogues of the Peptidic Neurotoxin, ω-Agatoxine IVB – an Experimental Point of View. Journal of Peptide Science 2008; 14() 267-277; doi:10.1002/psc.919

[57] Pringos E, Vignez M, Martinez J, Rolland V. Peptide neurotoxins that affect voltage-gated calcium channels: a close-up on ω-agatoxins. Toxins 2011; 3(1) 17-42; doi: 10.3390/toxins3010017

[58] Wilen CB, Tilton JC, Doms RW. Molecular Mechanism of HIV Entry. Advences in Experimental Medicine and Biology 2012; 726() 223-242; doi: 10.1007/978-1-4614-0980-9_10

[59] Vita C, Drakopoulou E, Vizzaviona J, Rochette S, Martin L, Ménez A, Roumestand C, Yang YS, Ylisastigui L, Benjouad J, Gluckman JC. Rational engineering of a miniprotein that reproduces the core of the CD4 site interacting with HIV-1 envelope glycoprotein. Proceedings of National Academy of Sciences of U. S. A. 1999; 96(23) 13091-13096; doi:10.1073/pnas.96.23.13091

[60] Li H, Guan Y, Szczepańska A, Moreno-Vargas AJ, Carmona AT, Robina I, Lewis GK, Wang LX. Synthesis and anti-HIV Activity of Trivalent CD4-Mimetic Miniproteins. Bioorganic and Medicinal Chemistry 2007; 15(12) 4220-4228; doi:10.1016/j.bmc. 2007.03.064

[61] Giardina DA, Gagliardi S, Martinelli M. Antagonists of the Neurokinin Receptors – Recent Patent Literature. Idrugs: the Investigational Drugs Journal 2003; 6(8) 758-772

[62] Seymour PA, Schmidt AW, Schulz DW. The Pharmacology of CP-154,526, a Non-peptide Antagonist of the CRH1 Receptor: a Review. CNS Drug Reviews 2003; 9(1) 57-96; doi:10.1111/j.1527-3458.2003.tb00244.x

[63] Nagamine J, Kawamura T, Tokunaga T, Huma WE, Nagata R, Nakagawa T, Taiji M. Synthesis and Pharmacological Profile of an Orally-active Growth Hormone Secreta-gogue, SM-130686. Combinatorial Chemistry and High Troughput Screening 2006; 9(3) 187-196; doi:10.2174/138620706776055548

[64] Chang RS, Lotti VJ, Monaghan RL, Birnbaum J, Stapley EO, Goetz MA, Albers-Schőnberg G, Patchett AA, Liesch JM, Hensens OD. Asperlicin, A Potent Nonpeptide CholecystokininAntagonist Selective for Peripheral Tissues Isolated from *Aspergillus alliaceus*. Science 1985; 230(4722) 177-179; doi:10.1126/science.2994227

[65] Huang F, Fu Y. A Review of Clinical Pharmacokinetics and Pharmacodynamics of Galantamine, a Reversible Acetylcholinesterase Inhibitor for the Treatment of Alzheimer s Disease, in Healthy Subjects and Patients. Current Clinical Pharmacology. 2010; 5(2) 115-124; doi:org/10.2174/157488410791110805

[66] Böhm H-J, Flohr A, Stahl M. Scaffold Hopping. Drug Discovery Today: Technologies. 2004; 1(3) 217-224; doi:10.1016/j.ddtec.2004.10.00

[67] Vainio MK, Kogej T, Raubacher F, Sadowski J. Scaffold Hopping by Fragment Re-placement. Journal of Chemical Information and Modeling. 2013; 53(7) 1825-1835; doi:10.1021/ci4001019

[68] Hruby VJ, Cai M, Design of Peptide and Peptidomimetic Ligands with Novel Phar-macological Activity Profiles. Annual Review of Pharmacology and Toxicology 2013; 53() 557-580; doi:10.1146/annurev-pharmtox-010510-100456

[69] Avan I, Hall CD, Katritzky A. Peptidomimetics via Modifications of Amino Acids and Peptide Bonds. Chemical Society Reviews 2014; 43(10) 3575-3594; doi:10.1039/C3CS60384A

[70] Zairi A, Tangy F, Bouassida K, Hani K. Dermaseptins and Magainins: Antimicrobial Peptides from Frogs' Skin—New Sources for a Promising Spermicides Microbicides —A Mini Review. Journal of Biomedicine and Biotechnology 2009; art. ID 452567, 8pp; doi: org/10.1155/2009/452567

[71] Porter EA, Wang X, Lee H-S, Weisblum B, Gellman SH. *Antibiotics: Non-haemolytic β-Amino-acid Oligomers. Nature* 2000; 404() 565; doi:10.1038/35007145

[72] Porter EA, Weisblum B, Gellman SH. Mimicry of Host-Defense Peptides by Unnatu-ral Oligomers: Antimicrobial β-Peptides. Journal of American Chemical Society 2002;124(25) 7324-7330; doi:10.1021/ja0260871

[73] Patch JA, Barron AE. Mimicry of Bioactive Peptides by via Non-natural Sequence-specific Peptidomimetic Oligomers. Current Opinion in Chemical Biology 2002; 6(6) 872-877; doi:10.1016/S1367-5931(02)00385-X

[74] Tew GN, Liu D, Chen B, Doerksen RJ, Kaplan J, Carroll PJ, Klein ML, DeGrado WF. *De Novo* Design of Biomimetic Antimicrobial Polymers. Proceedings of National Academy of Sciences of U.S.A. 2002; 99(8) 5110-51; doi:10.1073/pnas.082046199

[75] Lienkamp K, Madkour AE, Tew GN. Antibacterial Peptidomimetics: Polymeric Synthetic Mimics of Antimicrobial Peptides. Advances in Polymer Science 2013; 251() 141-172; doi:10.1007/12_2010_85

[76] Choi S, Isaacks A, Clemements D, Liu D, Kim H, Scott RW, Winkler JD, DeGrado WF. De Novo Design and In Vivo Activity of Conformationally Restrained Antimicrobial Arylamide Foldamers. Proceedings of National Academy of Sciences of U.S.A. 2009; 106 (17) 6968-6973; doi: 10.1073/pnas.0811818106

[77] Vagner J, Qu H, Hruby VJ. Peptidomimetics, a Synthetic Tool of Drug Discovery. Current Opinion in Chemical Biology 2008; 12(3) 292-296; doi:10.1016/j.cbpa.2008.03.009

[78] Wu CW, Seurynck SL, Lee KYC, Barron AE, Helical Peptidoid Mimics Lung Surfactant Prtein C. 2003; 10(11) 1057-1063; doi:10.1016/j.chembiol.2003.10.008

[79] Brown NJ, Johansson J, Barron AE, Biomimicry of Surfactant Protein C. Accounts of Chemical Research 2008; 41(10) 1409-1417; doi:10.1021/ar800058t

[80] Ramatahan R, Kamholz K, Fujii AM, Is there a Difference in Surfactant Treatment of Respiratory Distress Syndrome in Premature Neonates? A Review. Pulmonary and Respiratory Medicine 2013; S13, pp7; doi:org/10.4172/2161-105X.S13-004